General

Guideline Title

Bone health in patients with breast cancer.

Bibliographic Source(s)

Alberta Provincial Breast Tumour Team. Bone health in patients with breast cancer. Edmonton (Alberta): CancerControl Alberta; 2012 Nov. 22 p. (Clinical practice guideline; no. BR-010). [79 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Patients with Metastatic Breast Cancer

1. When to use bone-modifying agents (BMAs). In patients with metastatic breast cancer, BMAs are recommended upon confirmation of bone metastases; the presence of non-bone metastases is not an indication for the use of BMAs.
2. Which BMAs to consider and for how long.
    - For patients with breast cancer with bone metastases, no recommendations can be made favoring one agent over another. Acceptable agents and dosing regimens for bone metastases include:
        - Zoledronic acid: intravenous (IV) 4 mg over no less than 15 minutes, monthly
        - Pamidronate: IV 90 mg over no less than two hours, monthly
        - Clodronate: oral 1600 mg, daily
        - Denosumab: subcutaneous (SC) 120 mg, monthly

      Note: There are advantages and limitations to the different agents and routes of administration. The agent and route of administration should be left to the discretion of the treating physician, taking into account compliance with treatment, cost of treatment, and patient preference.

    - BMAs should be continued in patients with breast cancer with bone metastases until there is evidence of a substantial decline in performance status.
3. What to do after a skeletal-related event (SRE) or disease progression in bone. In patients with breast cancer with bone metastases, who have experienced an SRE or progression in bone metastases, switching from one BMA to another is currently not recommended, as there is no double-blind data to support this strategy.

Patients with Early Stage Breast Cancer

4. Fracture risk assessment and timing
    - Baseline bone mineral density (BMD) testing and fracture risk assessment is recommended for patients with early stage breast cancer for whom therapy with agents that suppress ovarian function is planned, including:
        - Premenopausal women with premature ovarian failure or ovarian suppression with luteinizing hormone releasing hormone analogue (LHRHA)
        - Postmenopausal women on aromatase inhibitors (AIs)
    - BMD testing in other postmenopausal women with early stage breast cancer is recommended according to the indications provided in the table below (Papaioannou et al., 2010).
    - BMD is calculated using a dual-energy x-ray absorptiometry (DEXA) scan.
    - Fracture risk should be assessed using the World Health Organization Fracture Risk Assessment Tool (FRAX; www.shef.ac.uk/FRAX/tool.jsp?locationValue=9).
    - Repeat BMD testing should be performed as follows, in patients for whom pharmacotherapy with BMAs is deemed to be not beneficial:
        - Low risk patients (10-year risk <10% based on FRAX score): every five years
        - Moderate risk patients (10-year risk 10%–20% based on FRAX score): every one to three years

Table. Canadian Guidelines on the Screening of Osteoporosis

Indications for Measuring Bone Mineral Density	
Older Adults (Age ≥50 Years)	*Younger Adults (Age <50 Years)*
Age ≥65 yr (both women and men)	Fragility fracture
Clinical risk factors for fracture (menopausal women, men age 50–64 years)	Prolonged use of glucocorticoids*
Fragility fracture after age 40 years	Use of other high-risk medications†
Prolonged use of glucocorticoids*	Hypogonadism or premature menopause (age <45 years)
Use of other high-risk medications†	Malabsorption syndrome
Parental hip fracture	Primary hyperparathyroidism
Vertebral fracture or osteopenia identified on radiography	Other disorders strongly associated with rapid bone loss and/or fracture
Current smoking	
High alcohol intake	
Low body weight (<60 kg) or major weight loss (>10% of body weight at age 25 years)	
Rheumatoid arthritis	
Other disorders strongly associated with osteoporosis	

Reproduced with permission from: Papaioannou A, Morin S, Cheung Am, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. Can Med Assoc J. 2010; 182:1864-1873.

*At least three months cumulative therapy in the previous year at a prednisone-equivalent dose ≥7.5 mg daily.

†For example, aromatase inhibitors or androgen deprivation therapy.

5. When to use BMAs, which agents to consider, and for how long
    - BMAs should be considered for the following patients with early stage breast cancer:
        - Premenopausal OR postmenopausal at high risk (i.e., 10-year fracture risk >20% OR prior fragility fracture of hip or spine OR more than 1 fragility fracture)
        - Postmenopausal at moderate risk (i.e., 10-year fracture risk 10%–20%) OR a T-score less than -2.0 AND undergoing

aromatase inhibitor therapy for breast cancer

- As per the Canadian Osteoporosis guidelines (Papaioannou et al., 2010), exercise, adequate calcium (1,200 mg per day total, diet plus supplements) intake, and vitamin D (1,000 IU per day) supplementation are also recommended.
- For patients with early stage breast cancer, no recommendations can be made favoring one BMA over another. Acceptable agents and dosing regimens for bone loss include:
  - Zoledronic acid: IV 4 mg over no less than 15 minutes every 6 to 12 months
  - Any oral bisphosphonate
  - Denosumab: SC 60 mg every 6–12 months

  Note: The route of administration should be left to the discretion of the treating physician, taking into account compliance with treatment, cost of treatment, and patient preference.

  - There is no data on the optimal duration of therapy with BMAs for patients with early stage breast cancer with treatment-related bone loss. Most randomized controlled trials have used durations of 2–3 years and none have compared one time period with another.
  - In patients with early stage breast cancer, there is no data to support a switch from one agent to another, following a skeletal-related event.

6. Monitoring for effectiveness. In patients with early stage breast cancer undergoing therapy with a BMA, BMD can be checked every two years. However, in patients with osteopenia, BMD should be checked annually.
7. Use of BMAs as adjuvant therapy. Outside of a clinical trial, BMAs are not recommended, for patients with early stage breast cancer, as a standard adjuvant therapy to improve recurrence or survival rates.

Patients with Metastatic or Early Stage Breast Cancer

8. Monitoring of adverse events. Patients undergoing therapy with BMAs should be aware that the most common adverse events include nausea, fatigue, arthralgia, back pain, pyrexia, bone pain, vomiting, anemia, diarrhea, dyspnea, extremity pain, and constipation (see Table 2 in the original guideline document).
   Patients should also be monitored for changes in renal function (i.e., creatinine clearance). In addition, patients with poor dental hygiene or poor dental health may be at increased risk of osteonecrosis of the jaw and should ideally consider undergoing preventive dentistry before starting treatment with a BMA. Adverse events should be managed with appropriate supportive care.

Clinical Algorithm(s)

An algorithm titled "Algorithm for the Use of Bone Modifying Agents in Patients with Breast Cancer with Bone Metastases or Treatment-induced Bone Loss" is provided in the original guideline document.

Scope

Disease/Condition(s)

- Metastatic breast cancer (bone metastases)
- Early-stage breast cancer
- Bone loss and symptoms of bone loss (treatment-related or cancer-related)

Guideline Category

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide evidence-based strategies for the management of bone loss and symptoms of bone loss in patients with a breast cancer diagnosis

Target Population

Patients who have been diagnosed with breast cancer and in whom bone metastases have been confirmed or those at risk of therapy-induced bone loss

Interventions and Practices Considered

1. Bone-modifying agents (BMAs)
    - Zoledronic acid
    - Pamidronate
    - Clodronate
    - Denosumab
2. Fracture risk assessment and bone mineral density (BMD) testing
3. Exercise, adequate calcium intake, and vitamin D supplementation
4. Monitoring therapy for effectiveness and adverse events

Major Outcomes Considered

- Bone mineral density (BMD)
- Bone turnover
- Fracture rates
- Survival (disease-free, relapse-free, and overall)
- Recurrence rates
- Skeletal-related events (SREs)
- Adverse events associated with therapy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (patient or population, intervention, comparisons, outcomes).

Guideline Questions

Patients with Metastatic Breast Cancer

1. When should bone-modifying agents (BMAs) be used in patients with metastatic breast cancer?
2. Which BMAs should be considered and for how long?
3. Should the BMA be switched after a skeletal-related event (SRE) or documentation of disease progression in bone?

Patients with Early Stage Breast Cancer

4. How should fracture risk be assessed and when for:
    - Premenopausal women with premature ovarian failure or ovarian suppression with luteinizing hormone releasing hormone analogue (LHRHA)
    - Postmenopausal women on aromatase inhibitors (AIs)
    - Other postmenopausal women with early stage breast cancer
5. Is there a role for BMAs in these populations and, if so, which agents should be considered and for how long?
6. How should treatment with BMAs be monitored for effectiveness?
7. Should BMAs be used as adjuvant therapy to improve breast cancer-related outcomes?

Patients with Metastatic or Early Stage Breast Cancer

8. When using BMAs, what potential adverse events should be disclosed to patients? What is the frequency of these adverse events with the different agents and schedules of administration? How should these adverse events be managed?

Search Strategy

A systematic search for relevant literature related to breast cancer and bone health was conducted of: MEDLINE (1950 to 2011 July) and EMBASE (1980 to 2012 July). The search included the terms *zoledronic acid* or *zoledronate* or *clodronate* or *clodronic acid* or *alendronate* or *alendronic acid* or *pamidronate* or *pamidronic acid* or *ibandronate* or *ibandronic acid* or *denosumab* and *breast neoplasm*. The MEDLINE and EMBASE search was limited to clinical trials, phase III, randomized controlled trials, and meta-analyses published in the English language.

Studies that were published prior to 1996 were excluded from the evidence tables. A total of 28 clinical trials were deemed relevant to the role of bisphosphonates and denosumab in the prevention of skeletal related events in patients with metastatic breast cancer; 11 clinical trials were deemed relevant to the role of bisphosphonates or denosumab in preventing recurrence or prolonging survival in metastatic breast cancer; and 21 clinical trials were deemed relevant to the role of bisphosphonates or denosumab for the treatment of hypercalcemia of malignancy in metastatic breast cancer.

In addition, the National Guideline Clearinghouse was searched for guidelines and systematic reviews related to breast cancer and bone health. A total of seven clinical practice guidelines that provided recommendations on the use of bisphosphonates in the setting of breast cancer were deemed relevant; these guidelines were developed by: the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), the International Society of Geriatric Oncology (ISGO), the European Expert Panel (EEP), and Cancer Australia. Following the initial literature search, an additional Canadian guideline, BONUS 6, was published by a panel of experts in the field and ASCO released an updated version of their guideline.

Number of Source Documents

- A total of 28 clinical trials were deemed relevant to the role of bisphosphonates and denosumab in the prevention of skeletal related events in patients with metastatic breast cancer; 11 clinical trials were deemed relevant to the role of bisphosphonates or denosumab in preventing recurrence or prolonging survival in metastatic breast cancer; and 21 clinical trials were deemed relevant to the role of bisphosphonates or denosumab for the treatment of hypercalcemia of malignancy in metastatic breast cancer.
- A total of seven clinical practice guidelines that provided recommendations on the use of bisphosphonates in the setting of breast cancer were deemed relevant.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team and a Knowledge Management (KM) specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This guideline was drafted by a medical oncologist with expertise in the area of bone health and breast cancer, with support from a Knowledge Management (KM) specialist. An expert panel consisting of medical oncologists, radiation oncologists, breast surgeons, and pathologists then reviewed the guideline and came to consensus on the recommendations.

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the KM Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook

(see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, Hanley DA, Hodsman A, Jamal SA, Kaiser SM, Kvern B, Siminoski K, Leslie WD, Scientific Advisory Council of Osteoporosis Canada. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010 Nov 23;182(17):1864-73. PubMed

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Optimization of bone health in patients with breast cancer

Potential Harms

Adverse events associated with bisphosphonate use (oral or intravenous) and denosumab are typically mild and manageable, but include arthralgia, fever, thrombosis, bone pain, fatigue/tiredness, nausea, and gastrointestinal symptoms. The frequencies of the most common adverse events is provided in Table 2 in the original guideline document. Patients undergoing therapy with bone modifying agents should be monitored throughout therapy for changes in renal function (i.e., creatinine clearance). In addition, patients with poor dental hygiene or poor dental health may be at increased risk of osteonecrosis of the jaw; therefore, patients should consider undergoing preventive dentistry before starting treatment with a bone modifying agent and avoid extensive dental work during therapy.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Breast Tumour Team. Bone health in patients with breast cancer. Edmonton (Alberta): CancerControl Alberta; 2012 Nov. 22 p. (Clinical practice guideline; no. BR-010). [79 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Nov

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Breast Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgeons, pathologists, psychosocial oncologists, nurses, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 12, 2014. The information was verified by the guideline developer on September 22, 2014.

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